The following recommendations are based on current medical evidence and expert opinion from clinicians. The content of the document is dynamic and will be revised as new clinical data becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient.

Criteria for Use for Leflunomide and Biologic Disease Modifying Anti-Rheumatic Drugs (DMARDs) in the Treatment of Moderate and Severe Rheumatoid Arthritis (RA)

VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel

Contents

I. Summary

Selection of DMARD(s) must take into account efficacy, approximate time to benefit, adverse events, ease of administration, and cost of the medication and monitoring. Individual patient factors such as aggressiveness of disease, structural damage, comorbid conditions, quality of life, and likelihood of compliance (i.e., oral administration versus patient's or caregiver's ability to inject subcutaneously versus clinic visits for intravenous infusion) must also be considered when making decisions regarding DMARD treatment. Patients who have contraindications to methotrexate (MTX) or who have had suboptimal disease control with MTX (with doses *up to* 25mg/week, *if tolerated*) due to lack of efficacy or toxicity may be eligible for the use of other DMARDs (i.e., leflunomide), including biologic agents (i.e., etanercept, infliximab, anakinra, or adalimumab) either as monotherapy or in combination with existing regimens. However, MTX as monotherapy or in combination with older DMARDs (i.e., oral/injectable gold, hydroxychloroquine, sulfasalazine, penicillamine, azathioprine) should be initiated in patients who have not received previous MTX treatment prior to considering use of leflunomide or a biologic agent.[1] FDA approved RA indications for leflunomide, etanercept, infliximab, anakinra, and adalimumab are listed in Table 1. A summary of efficacy determined from clinical trials of leflunomide, etanercept, infliximab, anakinra, and adalimumab are listed in Appendix I.

Randomized controlled trials have demonstrated the efficacy of leflunomide as an alternative to MTX as monotherapy in patients with contraindications to, intolerance to, or suboptimal response with MTX.[2-7] Leflunomide can also be used in combination with MTX if inadequate clinical response occurs despite full or maximally tolerated doses of MTX.[8-10] Patients with no previous treatment with MTX[2,3,7], no previous treatment with other DMARDs[2-5], and failure with previous DMARD therapy[2-4,6,8] showed improvement with leflunomide. The combined use of leflunomide with antimalarials, intramuscular or oral gold, D-penicillamine, or azathioprine has not been adequately studied.

Clinical trials have demonstrated the efficacy of etanercept[12-19], infliximab[21-31], anakinra[33-44], and adalimumab[46-52] in improving clinical signs and symptoms in patients with RA. Patients with early RA with no previous MTX treatment showed improvement with etanercept and infliximab.[16,17,31] Patients with active RA in whom previous DMARD therapy had failed showed improvement with etanercept, infliximab, and adalimumab.[12, 13, 21-23, 48, 52] All biologics have been shown to be beneficial when used in combination with MTX in patients with ongoing active RA despite adequate doses of MTX.[14,15,24-30,36,37,39,46,47,49] Infliximab is currently recommended for use only with concomitant MTX therapy.[24,32] Etanercept, anakinra, and adalimumab have been studied as monotherapy[12,13,16,17,19,33-35, 48, 52] as well as in combination with other DMARDs.[18, 38, 40-43, 50, 51] Serious infections have occurred with the concurrent use of etanercept and anakinra and therefore the combination of tumor necrosis factor (TNF) inhibitors and interleukin 1 (IL-1) receptor antagonists is not recommended.[18, 20, 32, 45, 53] Biologics should not be started or should be discontinued in patients with serious infections (Table 6).[20, 32, 45, 53] Previous tuberculosis (TB) may be reactivated in patients given TNF inhibitors; screening and prophylaxis according to local recommendations should be undertaken in patients with previous TB or patients at risk for developing TB (Table 5).[20,32,53]

In the absence of head to head clinical trials, there is no evidence that leflunomide or any one biologic should be used before another, or that any one of these agents is more effective than another. Choice will depend on individual patient presentation, past medical history, and comorbid conditions that may contraindicate use of one agent over another (Table 3) or may predispose the patient to safety risks (Table 4). Safety concerns with leflunomide (Table 7) include liver abnormalities, infections (i.e., interstitial pneumonia), and hematological abnormalities (i.e., pancytopenia), which may all be increased with the coadministration of MTX or other potentially immunosuppressive drugs.[11,64] Safety concerns with biologics (Table 7) include infection, malignancies (especially lymphoma), demyelinating disorders, CHF exacerbation, immunogenicity, autoantibodies and drug-induced lupus, and hematologic abnormalities.[54-73] (Appendix II contains "Dear Healthcare Provider" letters from the manufacturers of leflunomide, etanercept, and infliximab detailing important safety warnings.) Although leflunomide, etanercept, and infliximab have demonstrated effectiveness for the treatment of MTX naïve patients, use of these agents earlier in the treatment of RA should be limited due to long-term safety issues (Table 7) and cost (Table 8; Appendix III). However, patients with contraindications to all other DMARDs may use leflunomide, etanercept, or infliximab earlier (no data for anakinra or adalimumab in patients with early RA or without previous MTX treatment). Compared to leflunomide, disadvantages of biologic therapy include the need for parenteral administration (Table 2) and cost (Table 8; Appendix III).

The following recommendations are based on current medical evidence and expert opinion from clinicians. The content of the document is dynamic and will be revised as new clinical data becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient.

II. Criteria for Use

CRITERIA FOR ELIGIBILITY*:

1. Diagnosis of RA as defined by the American College of Rheumatology (ACR); *AND*
2. Active RA despite full and adequate treatment with ≥ 1 standard DMARDs at standard or maximally tolerated dose; *AND*
3. Baseline monitoring parameters within normal limits (See Table 5).

Consider LEFLUNOMIDE…

As MONOTHERAPY if:
- Documented contraindications, intolerance (toxicity) and/or suboptimal response to an adequate trial of MTX; *AND*
- Documented contraindications, intolerance and/or suboptimal response to ≥ 1 standard DMARDS at standard target dose (unless significant toxicity limited the dose tolerated), regardless of whether they were prescribed sequentially or in combination: oral/injectable gold, hydroxychloroquine, sulfasalazine, penicillamine, azathioprine.

As COMBINATION THERAPY with MTX if:
- Documented suboptimal response with full or maximally tolerated doses of MTX

Consider a BIOLOGIC (etanercept, infliximab, anakinra, adalimumab)…

As MONOTHERAPY if:
- Documented contraindications, intolerance (toxicity) and/or suboptimal response to an adequate trial of MTX; *AND*
- Documented contraindications, intolerance and/or suboptimal response to ≥ 1 standard DMARDS at standard target dose (unless significant toxicity limited the dose tolerated), regardless of whether they were prescribed sequentially or in combination: oral/injectable gold, hydroxychloroquine, sulfasalazine, penicillamine, azathioprine, leflunomide

As COMBINATION THERAPY with MTX if:
- Documented suboptimal response with full or maximally tolerated doses of MTX

**** Each patient's risk versus benefit should be carefully considered before initiating therapy (or continuing therapy) in instances where safety and efficacy have not been established (See Table 4). Choice of therapy should be based on physician discretion and clinical judgment.***

CRITERIA FOR EXCLUSION:

1. MTX naïve – If a patient has failed to demonstrate an adequate response to a single DMARD other than MTX, MTX should be initiated with doses *up to* 25mg/week (*as tolerated*) for at least 3 months, with or without other DMARDs; *OR*
2. If a patient has previously achieved remission on a given DMARD, he or she should be restarted on this previously effective DMARD prior to use of leflunomide, etanercept, infliximab, anakinra, or adalimumab; *OR*
3. Contraindications to leflunomide, etanercept, infliximab, anakinra, or adalimumab. (See Table 3).

CRITERIA FOR CONTINUATION:

After initiation of an agent, adequate response with decreased disease activity such as improvement in severity of affected joints or resolution of flares/decrease in flares (within 4-12 weeks for leflunomide; within 8-12 weeks for etanercept, infliximab, and adalimumab; within 2-16 weeks for anakinra) based on clinical judgment and quantitative measurements, including:

1. Improvement in validated quantitative measures of response such as visual analog scales (VAS), Likert scales, joint tenderness and/or swelling, and laboratory data (ESR, CRP); *AND*
2. Improvement in the DAS score ≥ 1.2; *OR*
3. Achievement of a DAS28 score of < 3.2; *OR*
4. > 20% improvement according to ACR 20% response criteria
5. Monitoring parameters at follow-up *MUST* be within normal limits (See Table 5).

CRITERIA FOR WITHDRAWAL OF THERAPY:

1. Inefficacy - Inadequate response (despite confirmed compliance) within 8-16 weeks after starting treatment at the recommended dosing schedule (See Table 2); *OR*
2. Loss of efficacy/unacceptable disease activity – Ongoing disease activity after 3 months of maximum therapy despite confirmed compliance (i.e., Repetitive flares; progressive joint damage); *OR*
3. Development of drug-related toxicity or adverse events (See Tables 6 and 7).

III. TABLES [11,20,32,45,53]

Table 1. FDA-Approved Rheumatoid Arthritis Indications [11,20,32,45,53]

Moderately to severely active RA	Reduction of signs and symptoms	Inhibition of progression of structural damage	Improvement in physical function	Induction of major clinical response	Monotherapy	Combination Therapy	Use after inadequate response to ≥1DMARDS	Use in patients who have not previously failed treatment with a DMARD
	Leflunomide (1998)	Leflunomide (1998)	Leflunomide (2003)					
Etanercept (1998)	Etanercept (1998)	Etanercept (2000)	Etanercept (2003)	Etanercept (2004)	Etanercept	Etanercept (with MTX)	Etanercept	Etanercept (2000)
Infliximab (1999)	Infliximab (1999)	Infliximab (2000)	Infliximab (2002)			Infliximab (with MTX)	Infliximab (inadequate response to MTX)	Infliximab (2004; can be used in patients not previously treated with MTX)
Anakinra (2001)	Anakinra (2001)	Anakinra (2003)			Anakinra	Anakinra (with DMARDs other than TNF antagonists)		
Adalimumab (2002)	Adalimumab (2002)	Adalimumab (2002)	Adalimumab (2004)		Adalimumab	Adalimumab (with MTX or other DMARDs)	Adalimumab	

Table 2. FDA-Approved Dosing and Administration [11,20,32,45,53]

	Leflunomide	Etanercept	Infliximab	Anakinra	Adalimumab
Initial Dose	100mg daily for 3 days; optional if used in combination with MTX	Not Applicable	3mg/kg over 2 hours at weeks 0, 2, 6 in combination with MTX	Not Applicable	Not Applicable
Maintenance Dose	20mg/day; if not well tolerated clinically, the dose may be decreased to 10 mg daily	25mg twice weekly (as 2 separate injections 72-96 hours apart); 50mg once weekly (as one injection)	3mg/kg over 2 hours every 8 weeks in combination with MTX	100mg/day administered at approximately the same time every day; 100mg every other day for patients with creatinine clearance < 30mL/min	40mg every other week
Route of Administration	Oral	Subcutaneous	Intravenous	Subcutaneous	Subcutaneous
Time to Benefit	4-12 weeks	8-12 weeks	8-16 weeks	2-16 weeks	12 weeks
Maximum Dose	20 mg/day	50mg per week	10mg/kg over 2 hours every 8 weeks in combination with MTX; **or** treating every 4 weeks	100mg/day	40mg every week if not taking concomitant MTX
Dose Adjustments for Special Populations	10mg/day for ALT between 2- & 3-fold ULN; discontinue if persistent ALT between 2- & 3-fold ULN despite dose reduction or if > 3-fold ULN	Not Applicable	Not Applicable	100mg every other day for patients with renal insufficiency or end-stage renal disease (creatinine clearance < 30mL/min)	Not Applicable

Table 3. Contraindications[11,20,32,45,53]

Leflunomide	Etanercept	Infliximab	Anakinra	Adalimumab
Hypersensitivity to leflunomide or other components of leflunomide Pregnancy (Category X)	Sepsis Hypersensitivity to etanercept or any of its components Active infections including chronic or localized infections	Doses > 5mg/kg in patients with moderate-severe heart failure (NYHA Class III/IV) Hypersensitivity to murine proteins or any component of infliximab Clinically important, active infection	Hypersensitivity to E-coli-derived proteins, anakinra, or any component of the product Active infections	Hypersensitivity to adalimumab or any of its components Active infections, including chronic and localized infections

Table 4. Precautions[11,20,32,45,53]

Leflunomide	Etanercept	Infliximab	Anakinra	Adalimumab
Chronic renal insufficiency – free fraction doubled Hepatic insufficiency, Hepatitis B, Hepatitis C Severe immunodeficiency Bone marrow dysplasia Severe, uncontrolled infections Vaccination with live vaccines Hepatotoxic drugs (NSAIDs, tolbutamide, rifampin, warfarin) Elderly patients (>65 years) – increased risk of infection Nursing mothers Men wishing to father a child Pediatric patients with body weights $\leq$ 40KG – reduced clearance of metabolite	H/o recurring infections or underlying conditions which may predispose patients to infections, such as advanced or poorly controlled diabetes Concomitant use with anakinra – increased rate of infection Pre-existing or recent onset of central nervous system (CNS) demyelinating disorders H/o significant hematologic abnormalities Heart failure H/o malignancy Vaccination with live vaccines – no data on secondary transmission of infection Elderly population – increased risk of infections Pregnancy (Category B) Nursing mothers	Chronic infection or h/o recent infection Endemic area for histoplasmosis or coccidioidomycosis Concomitant use with anakinra Ongoing or h/o significant hematologic abnormalities Pre-existing or recent onset of CNS demyelinating or seizure disorders Heart failure H/o malignancy Vaccination with live vaccines Elderly (>65 years) – increased risk of infection Pregnancy (Category B) Nursing mothers	Immunosuppressed patients – safety and efficacy unknown Chronic infections – safety and efficacy unknown Concomitant treatment with etanercept (higher rate of infection) or other TNFα inhibitor (use not established) Vaccination with live vaccines Impaired renal function (plasma clearance reduced) Neutropenia Elderly ($\geq$65 years) – higher risk for infection Pregnancy (Category B) Nursing mothers	H/o recurrent infections or underlying conditions which may predispose to infections Endemic regions for tuberculosis and histoplasmosis Concomitant treatment with anakinra – possible increased risk of infection Pre-existing or recent onset CNS demyelinating disorders Heart failure H/o malignancy Immunosuppressed patients – safety and efficacy not evaluated Vaccination with live vaccines Elderly (>65 years) – increased risk of infection Pregnancy (Category B) Nursing mothers

Table 5. Monitoring Parameters[11,20,32,45,53, 99-110]

	Leflunomide	Etanercept	Infliximab	Anakinra	Adalimumab
Baseline	CBC (including differential WBC and PLT, Hgb, Hct); LFTs; Hep B and Hep C serologies; Scr; Infections; Screen for TB; Pregnancy	Screen for TB; Infections; Heart Failure; CBC; LFTs	Screen for TB; Infections; Heart Failure; CBC; LFTs; Hep B serologies;	CBC; Infections; Screen for asthma	Screen for TB; Infections; Heart Failure; CBC; LFTs
Follow-up	CBC every month for the first 6 months, followed by every 6-8 weeks thereafter; if using in combination with MTX and/or other potential immunosuppressive agents, monthly monitoring of LFTs are required LFTs (ALT at minimum) monthly for the first 6 months, and then, if stable, every 6-8 weeks thereafter; if using in combination with MTX, monthly monitoring of LFTs (ALT, AST, and albumin) are required - For mild increase in LFTs but < 2-fold ULN, repeat testing in 2-4 weeks - For values > 2-fold ULN but < 3-fold ULN, decrease dose with close monitoring every 2-4 weeks - If persistent > 2-fold ULN but < 3-fold ULN, or > 3-fold ULN, discontinue leflunomide and administer washout S/sx infection – if infection present, discontinue leflunomide and administer washout If discontinue leflunomide or switch to another agent, continue to monitor closely due to long half-life of leflunomide New onset or worsening pulmonary symptoms, such as cough and dyspnea, with or without associated fever New onset or worsening neuropathy symptoms	S/sx new infection S/sx new onset CHF or CHF exacerbation CBC LFTs	S/sx new infection S/sx liver dysfunction; Hep B S/sx Blood dyscrasias (i.e., persistent fever) S/sx new onset CHF or CHF exacerbation CBC LFTs	CBC every month for 3 months, then every 4 months for up to 1 year	S/sx new infection S/sx Blood dyscrasias (i.e., persistent fever, bruising, bleeding, pallor) S/sx new onset CHF or CHF exacerbation CBC LFTs

Table 6. Discontinuation Criteria[11,20,32,45,53, 99-110]

Leflunomide	Etanercept	Infliximab	Anakinra	Adalimumab
Development of a serious infection Evidence of bone marrow suppression Persistent elevation of ALT > 2-fold ULN but < 3-fold ULN, or ALT > 3-fold ULN Stevens-Johnson syndrome Toxic epidermal necrolysis New onset or worsening pulmonary symptoms, such as cough and dyspnea, with or without associated fever New onset or worsening neuropathy symptoms Desire to conceive (men and women) Washout Procedure upon discontinuation of leflunomide: 1. Administer cholestyramine 8 grams TID for 11 days. (The 11 days do not need to be consecutive unless there is a need to lower the plasma level rapidly.) 2. Verify plasma levels less than 0.02mg/L by 2 separate tests at least 14 days apart. If plasma levels are higher than 0.02mg/L, additional cholestyramine treatment should be considered.	Development of serious infection or sepsis Anaphylactic reaction or other serious allergic reaction Significant exposure to Varicella virus Significant CNS adverse reactions S/sx of lupus-like syndrome New onset or worsening symptoms of heart failure Significant hematologic abnormalities Significant hepatic abnormalities	Development of serious infection Development of jaundice or marked liver enzyme elevations (≥ 5X ULN) New onset or worsening symptoms of heart failure Significant hematologic abnormalities Hypersensitivity reactions Significant CNS adverse reactions Development of lupus-like syndrome	Development of serious infection Severe hypersensitivity reaction Significant hematologic abnormalities	Development of serious infection Anaphylactic or serious allergic reaction Confirmed significant hematologic abnormalities Development of s/sx lupus-like syndrome New onset or worsening symptoms of heart failure Significant hepatic abnormalities

Table 7. Adverse Events and Safety Information[11,20,32,45,53, 54-73]

	LEFLUNOMIDE	ETANERCEPT	INFLIXIMAB	ANAKINRA	ADALIMUMAB
TUBERCULOSIS	_____	38 reports (53% in US; 47% outside of US) out of 150,000 patients treated (90% use in US; 10% use outside of US) in 230,000 approximate patient-years of exposure; 11.2 months median time to onset; 50% extrapulmonary/miliary (Data through 2002)	FDA Med Watch data from 1998 – May 29, 2001: 70 cases reported; 12 week median onset; 48 cases with 3 or less doses; 40 cases had extrapulmonary disease; 33 cases confirmed biopsy. As of 11/2001, FDA had received 117 reports of infliximab associated-TB. Background rate of TB in pts with RA in US = 6.2 cases/100,000 pt-years. Rate of TB with infliximab = 24.4 cases per 100,000 pt-years _____ 172 reports (32% in US; 68% outside of US) out of 200,000 patients treated (64% use in US; 36% use outside of US) in 230,000 approximate patient-years of exposure; 75% had onset by 6 weeks, 97% by 7 months; 45% extrapulmonary/military (Data through 2002)	1 case reported with more than 19,000 patient-years of exposure through May 2003	13 reports (23% use in US; 77% use outside of US) out of 2500 patients treated (60% use in US; 40% use outside of US) in 4900 approximate patient-years of exposure; onset in 3-8 months; 40% extrapulmonary /military involvement (Data from all clinical trials)
OTHER INFECTIONS	80 cases of interstitial pneumonia out of ~ 400,000 patients receiving leflunomide worldwide	FDA AERS database search from 1998- 3rd quarter 2002 N=113, 000 Aspergillosis = 10 Candidiasis = 8 Cryptococcosis = 8 Histoplasmosis = 3 Listeria monocytogenes = 2 Nocardiosis = 1 Mycobacterium species = 7 FDA also reports: Coccidioidomycosis = 1 Cytomegalovirus = 8 Infectious mononucleosis = 5 Pneumocystis carnii = 5	FDA AERS database search from 1998-3rd quarter 2002 Aspergillosis = 29 Candidiasis = 38 Cryptococcosis = 11 Histoplasmosis = 39 Listeria monocytogenes = 36 Nocardiosis = 10 Mycobacterium species = 30 FDA also reports: Coccidioidomycosis = 13 Cytomegalovirus = 20 Infectious mononucleosis = 12 Pneumocystis carnii = 44	No cases of mycobacterium tuberculosis, pneumocystis, listeria, or histoplasmosis seen during all clinical trials. Fungal, mycobacterial, and bacterial infections were reported in post-marketing setting.	6 cases caused by histoplasma, aspergillus, and nocardia were reported in clinical trials.
CNS DEMYELINATION	_____	17 cases temporally related to anti-TNF treatment; partial or complete resolution on discontinuation. Signs/symptoms included confusion, visual loss, parasthesias, progressive weakness, and bladder/bowel difficulties.	2 cases temporally related to anti-TNF treatment; partial or complete resolution on discontinuation. Signs/symptoms included confusion, visual loss, parasthesias, progressive weakness, and bladder/bowel difficulties.	Not associated with these complications	4 cases: 1 = optic neuritis; 3 = parasthesias; 3 out of 4 resolved with discontinuation of therapy
CONGESTIVE HEART FAILURE	_____	RENAISSANCE – conducted by Immunex in North America; ~ 900 subjects 12.7 months median follow-up RECOVER – conducted by Wyeth in Europe, Israel, Australia, New Zealand; ~ 100 subjects 5.7 months median follow-up Both phase II/III, multicenter, placebo-controlled, double-blind, randomized controlled trials Studies halted after pre-specified analysis determined that the study was unlikely to demonstrate benefit. **RENAISSANCE vs RECOVER** Age: 62.3 years / 64.6 years Gender: 78% Male / 78% Male Race: 84% Caucasian / 99% Caucasian CHF duration: 5.6 years / 4.5 years ↑ CHF sx: Up to 27% / Up to 13% Post-Marketing reports to the FDA of CHF through February 2002: 51 cases (30 = etanercept; 21 = infliximab);	ATTACH – Phase II, pilot trial; randomized, double-blind, placebo-controlled, multicenter trial (32 centers in US); ~ 149 subjects 16 deaths total; 7 due to worsening CHF Post-Marketing reports to the FDA of CHF through February 2002: 51 cases (30 = etanercept; 21 = infliximab); 42 new-onset CHF, 9 CHF exacerbation Median age = 64 years Median time to onset = 3.5 months 10 cases (20%) were < 50 years old → 4 etanercept; 6 infliximab; After discontinuation of TNFα antagonists and heart failure treatment, 3 resolved, 6 improved, and 1 died.	_____	Not known. No trials in severe heart failure have been performed due to observed increase in morbidity and mortality in other trials of TNFα antagonists in patients with moderate to severe heart failure (grade II-IV). Patients with controlled CHF were not excluded in pivotal trials, and no CHF exacerbations were seen.

		42 new-onset CHF, 9 CHF exacerbation Median age = 64 years Median time to onset = 3.5 months 10 cases (20%) were < 50 years old → 4 etanercept; 6 infliximab; After discontinuation of TNFα antagonists and heart failure treatment, 3 resolved, 6 improved, and 1 died.			
MALIGNANCIES	_____	Controlled portions of controlled trials: Etanercept = 12 cases among 2502 patients; 0.5 mean years exposure Placebo = 5 cases among 921 patients; 0.5 mean years exposure All clinical trials: 55 cases among 3389 patients; 2.2 mean years exposure; SIR 0.98 (CI = -0.5, 1.5)	Controlled portions of controlled trials: Infliximab = 22 cases among 2421 patients; 1.0 mean year exposure Placebo = 1 case among 489 patients; 0.9 mean years exposure All clinical trials: 27 cases among 2421 patients; 1.7 mean years exposure; SIR 1.15 (CI = 0.76, 1.67)	In all RA studies: Anakinra =21 cases (non-Hodgkin's lymphoma) among 2531 patients (exposure = 1873 patient-years); rate = 1.12 per patient-year _____ Among 5300 RA patients treated with anakinra in clinical trials for a mean of 15 months (approximately 6400 patient-years of data), 37 malignancies other than lymphoma were reported. Most common observed were of the breast, respiratory system, and digestive system.	Controlled portions of controlled trials: Adalimumab = 8 cases among 1380 patients; 0.6 mean years exposure Placebo = 0 cases among 690 patients; 0.5 mean years exposure All clinical trials: 46 cases among 2468 patients; 2 years median exposure; SIR 1.0 (CI = 0.7, 1.3)
LYMPHOMA	_____	Controlled portions of controlled trials: Etanercept = 1 case among 2502 patients; 0.5 mean years exposure Placebo = 0 cases among 921 patients; 0.5 mean years exposure All clinical trials: 6 cases among 3389 patients; 2.2 mean years exposure; SIR 2.31 (CI = 085, 5.03) 18 cases occurring after the initiation of etanercept therapy were reported to the FDA between May 1999 – December 2000. 95,500 etanercept users in the US through 2001 as estimated by manufacturer. Lymphoma rate among US residents = 18/95, 500, or ~ 19/100,000 treated persons. From January 1999 – December 2002, there were 63 reports to the FDA with biopsy-proven lymphoma diagnosed subsequent to etanercept therapy.	Controlled portions of controlled trials: Infliximab = 3 cases among 2421 patients; 1.0 mean year exposure Placebo = 0 cases among 489 patients; 0.9 mean years exposure All clinical trials: 6 cases among 2421 patients; 1.7 mean years exposure; SIR 6.89 (CI = 2.56, 15.19) 8 cases occurring after the initiation of infliximab therapy were reported to the FDA between May 1999 – December 2000. 121,000 infliximab users in the US through 2001 as estimated by manufacturer. Lymphoma rate among US residents = 8/121, 000, or ~ 6.6 cases/100,000 treated persons. From January 1999 – December 2002, there were 95 reports to the FDA with biopsy-proven lymphoma diagnosed subsequent to infliximab therapy.	In all RA studies: Anakinra = 1 case (non-Hodgkin's lymphoma) among 2531 patients (exposure = 1873 patient-years); rate = 0.05 per patient-year _____ Among 5300 RA patients treated with anakinra in clinical trials for a mean of 15 months (approximately 6400 patient-years of data), 8 lymphomas were observed for a rate of 0.12 cases per patient-years (3.6 – fold higher than the rate of lymphoma expected for the general population.	Controlled portions of controlled trials: Adalimumab = 2 cases among 1380 patients; 0.6 mean years exposure Placebo = 0 cases among 690 patients; 0.5 mean years exposure All clinical trials: 10 cases among 2468 patients; 2 years median exposure; SIR 5.42 (CI = 2.6, 10.0)
LIVER REACTIONS	296 cases of hepatic reactions in the first 104,000 patient-years exposure have been reported by the European Agency for the Evaluation of Medicinal Products (EMEA) as of March 2001. 129 were considered serious → 2 cases of liver cirrhosis and 15 cases of liver failure with 9 fatal outcomes	19 cases reported to FDA Med Watch	31 cases reported to FDA Med Watch _____ 3 patients in controlled trials and 35 patients in the post marketing setting with severe hepatic reactions among 576,000 patients worldwide treated with infliximab since August 1998. Hepatic reactions included: acute liver failure, jaundice/cholestasis, and hepatitis	_____	5% of patients treated with adalimumab experienced an increase in alkaline phosphatase as compared with 3% receiving placebo.
HEMATOLOGIC ABNORMALITIES	16 cases of pancytopenia among 76,100 patients treated worldwide (since September 1998 – October	2 cases of aplastic anemia; 2-4 month onset from initiation of etanercept therapy; no other immunosuppressive medications; no prior history of blood dyscrasias; outcome = death 7 cases of pancytopenia; 2 week-3 month onset	15 cases of pancytopenia in post marketing setting	0.4% of patients receiving anakinra developed neutropenia (ANC < 1 X 10^9/L).	Agranulocytosis, granulocytopenia, leukopenia, pancytopenia, polycythemia, and thrombocytopenia

	1999) reported by the EMEA in October 1999	from initiation of etanercept therapy; most with current or prior use of another immunosuppressive agent; most with no history of blood dyscrasias; 4 recovered, 3 deaths. These cases confounded by other risk factors (concomitant medications and infection)		2% of patients receiving concomitant anakinra and etanercept treatment developed neutropenia.	reported with an occurrence of <5%.
AUTO-ANTIBODIES AND DRUG-INDUCED LUPUS	_____	4 reports of cutaneous lupus-like skin rashes with positive autoantibodies temporally associated with starting etanercept. None associated with systemic signs and symptoms of SLE and were not diagnosed as SLE. This lead to label change in January 2001. As of 2002, 22 case reports of lupus-like syndromes have been reported.	ATTRACT trial = 62% of infliximab-treated patients compared with 27% of placebo-treated patients developed positive ANA; 16% of infliximab patients compared with 0% on placebo developed anti-ds DNA antibodies. Lupus and lupus-like syndromes reported.	_____	12% rate of positive ANA compared with 7% placebo. 1 patient out of 2334 developed signs and symptoms of new-onset lupus-like syndrome that improved upon discontinuation of therapy.
IMUNOGENICITY	_____	6% incidence to TNF receptor portion or other protein components. All were non-neutralizing. Antibody development was not associated with clinical response or adverse events.	10% incidence of human anti-chimeric antibodies. Patients with positive test for antibodies have a 2-3 fold greater risk of experiencing an infusion-related reaction. Concurrent use of immunosuppressant agents reduces antibody formation and likelihood of an infusion reaction.	49% of patients in clinical trials tested positive for anti-anakinra antibodies. 2% were positive for antibodies capable of neutralizing the biologic effect of anakinra. Antibody development was not associated with adverse events.	5% (58/1062) of RA patients developed antibodies to adalimumab. These were neutralizing in vitro. Patients concomitantly receiving MTX had lower antibody development (1%) than adalimumab monotherapy (12%). Antibody development was not correlated with adverse events. ACR response was lower in antibody –positive patients than antibody negative patients.

Table 8. Acquisition Costs[74]

**** Costs as reported below reflect current pricing only. Please refer to the PBM website (vaww.pbm.med.va.gov or www.vapbm.org) for updated cost information.***

Product	Dose	Schedule	Cost per dispensing unit	Cost/ Patient /Year ($)
Adalimumab (Humira ®)	40 mg	Every other week	$687.74/2 single-use syringes (40mg/1ml syringe)	$8,940.62
Adalimumab(Humira ®)	40 mg	Weekly	$687.74/2 single-use syringes (40mg/1ml syringe)	$17,881.24
Anakinra (Kineret®)	100 mg	Once daily	$789.80/28 single-use syringes (100mg/1ml syringe)	$10,267.40
Etanercept (Enbrel®)	25mg	Twice weekly	$360.06/4 SDV (25mg/vial)	$9,361.56
Etanercept (Enbrel®)	50mg	Once weekly	$720.12/4 SDV (50mg/vial)	$9,361.56
Infliximab (Remicade®) +	3 mg/kg	Once every 8 weeks	$388.31/20ml vial (100mg/20ml vial)	<70kg $6,989.58 - $10,484.37 >70kg $10,484.37 - $13,979.16
Infliximab (Remicade®)+	10 mg/kg	Once every 8 weeks	$388.31/20ml vial (100mg/20ml vial)	<70kg $20,968.74 - $24,463.53 >70kg $24,463.53 - $27,958.32
Leflunomide (Arava®)	100 mg; 20mg	Once daily for 3 days (loading dose); Once daily	$ 162.44/ 30 tablets (20mg/tablet)	$2,034.65
Leflunomide (Arava®)	10 mg	Once daily (not including loading dose)	$162.34/30 tablets (10mg/tablet)	$1969.73
Methotrexate‡	25 mg	Weekly	$.23 - $.63 per tablet (2.5 mg tabs)	$ 119.60 - $327.60

SDV = single dose vials
+ Costs include infusion at weeks 0, 2,6,14,22,30,38,46,54; 3mg/kg: <70kg 2-3 vials, >70kg 3-4 vials; 10mg/kg: <70kg 6-7 vials, >70kg 7- 8 vials
‡ Methotrexate included to calculate combination therapy costs

IV. APPENDICES

Appendix I. Efficacy Results

Reference	Trial	No. of subjects	End Point	Treatment Group	ACR 20%	ACR 50%	ACR 70%
Leflunomide							
Strand et al.[2] (US301)	Monotherapy	485	52 weeks	Leflunomide 20mg/day Placebo MTX	52 26 46	34 8 23	20 4 9
Cohen et al.[3] (US301)	Monotherapy (extension trial)	235	24 months	Leflunomide 20mg/day MTX	79 67	56 43	26 2
Smolen et al.[5] (MN301)	Monotherapy	358	24 weeks	Leflunomide 100mg/day X 3 days; then 20mg/day Placebo Sulfasalazine 500mg/day, increased to 2000mg/day	55 29 56	33 14 30	10 2 8
Emery et al.[6] (MN302/304)	Monotherapy	999	52 weeks (year 1) 104 weeks (year 2)	Leflunomide 100mg/day X 3 days; then 20mg/day MTX Leflunomide 100mg/day X 3 days; then 20mg/day MTX	51 64.4 64.6 76.7	31.1 43.8	9.9 16.4
Weinblatt et al.[8]	Combination therapy	30	52 weeks	Leflunomide 100mg X 2 days; then 10mg/day (inc to 20mg/day PRN) + MTX	50	35	4
Kremer et al.[9]	Combination therapy	263	24 weeks	Leflunomide 100mg X 2 days; then 10mg/day (inc to 20mg/day PRN) + MTX Placebo + MTX	42.2 19.5	26.2 6.0	10.0 2.3
Kremer et al.[10]	Combination therapy (extension trial)	192	24 weeks	Leflunomide 100mg X 2 days; then 10mg/day (inc to 20mg/day PRN) + MTX Leflunomide 100mg X 2 days; then 10mg/day (inc to 20mg/day PRN) + MTX *[Previously placebo+MTX group]*	56.3 58.3	35.4 28.1	16.7 11.5
Etanercept							
Moreland et al.[12]	Monotherapy	180	3 months	Etanercept 0.25mg/m^2 Etanercept 2 mg/m^2 Etanercept 16 mg/m^2 Placebo	33 46 75 14	9 22 57 7	
Moreland et al.[13]	Monotherapy	234	26 weeks	Etanercept 10mg Etanercept 25 mg Placebo	51 59 11	24 40 5	9 15 1
Weinblatt et al.[14]	Combination therapy	89	24 weeks	Etanercept 25 mg + MTX Placebo + MTX	71 27	39 3	15 0
Kremer et al.[15]	Combination therapy	79	3 years	Etanercept 25 mg + MTX	77	47	23
Bathon et al.[16]	Monotherapy in Early RA	632	12 months	Etanercept 10mg + Placebo Etanercept 25mg + Placebo MTX + Placebo	61 72 65	32 49 43	16 25 22
Genovese et al.[17]	Monotherapy in Early RA (extension)	512	2 years	Etanercept 10mg + Placebo Etanercept 25mg + Placebo MTX + Placebo	61 72 59	35 49 42	19 29 24
Genovese et al.[18]	Combination therapy (with Anakinra)	244	6 months	Etanercept 25mg BIW + Placebo Etanercept 25mg once weekly + Anakinra 100mg Etanercept 25mg BIW+ Anakinra 100mg	68 51 62	41 39 31	21 24 14
Keystone et al.[19]	Monotherapy (once weekly)	420	16 weeks	Etanercept 50mg QW + Placebo Etanercept 25mg BIW Placebo	55 63		
Infliximab							

Maini et al.[25] ATTRACT	Combination therapy	428	30 weeks	3mg/kg Q8W + MTX 3mg/kg Q4W + MTX 10mg/kg Q8W + MTX 10mg/kg Q4W + MTX Placebo + MTX	50 52 51 58 20	27 29 31 26 5	8 11 18 11 0
Lipsky et al.[26] (Abstract)	Combination therapy (extension)	428	54 weeks	3mg/kg Q8W + MTX 3mg/kg Q4W + MTX 10mg/kg Q8W + MTX 10mg/kg Q4W + MTX Placebo + MTX	42 28 59 59 17	21 35 40 38 9	11 18 26 19 3
Lipsky et al.[27]	Combination therapy (extension)	428	54 weeks	3mg/kg Q8W + MTX 3mg/kg Q4W + MTX 10mg/kg Q8W + MTX 10mg/kg Q4W + MTX Placebo + MTX	42 48 59 59 17	21 34 39 38 8	10 17 25 19 2
Lipsky et al.[28] (Abstract)	Combination therapy	428	54 weeks	3mg/kg Q8W + MTX 3mg/kg Q4W + MTX 10mg/kg Q8W + MTX 10mg/kg Q4W + MTX Placebo + MTX	40.7 39.5 48.3 42 15.9		
Maini et al.[29]	Combination therapy	428 – year 1 259 – year 2	102 weeks	3mg/kg Q8W + MTX 3mg/kg Q4W + MTX 10mg/kg Q8W + MTX 10mg/kg Q4W + MTX Placebo + MTX	42 40 48 40 16	21 30 36 20 6	10 21 20 10 1
Kavanaugh et al.[30]	Combination therapy	19	12 weeks – pilot 40 weeks – open label	Pilot = 5mg/kg + MTX 10mg/kg + MTX 20mg/kg + MTX Placebo + MTX Open = 10mg/kg + MTX	 43 57 57 14 58	 29 14 43 14 73	
St Clair et al.[31]	Combination therapy	1049	54 weeks	3mg/kg + MTX 6mg/kg + MTX Placebo + MTX	62.4 66.2 53.6	45.6 50.4 32.1	32.5 37.2 21.2
Anakinra							
Bresnihan et al.[33]	Monotherapy	472	24 weeks	30mg QD 75mg QD 150mg QD Placebo	39* 34* 43* 27* *ACR Composite Score only	*ACR Composite Score only	*ACR Composite Score only
Nuki et al.[35]	Monotherapy	309	52 weeks	From group receiving Anakinra: 30mg QD 75mg QD 150mg QD From group receiving placebo: 30mg QD 75mg QD 150mg QD	 41 51 47 51 47 46		
Cohen et al.[36]	Combination therapy	419	24 weeks	0.04mg/kg + MTX 0.1mg/kg + MTX 0.4mg/kg + MTX 1mg/kg + MTX 2mg/kg + MTX Placebo + PTX	19 30 36 42 35 23	13 20 11 24 17 4	5 7 2 10 7 0
Adalimumab							
Weinblatt et al.[46] ARMADA	Combination therapy	271	24 weeks	20mg QOW + MTX 40mg QOW + MTX 80mg QOW + MTX	47.8 62.7 65.8	31.9 55.2 42.5	10.1 26.9 19.2

				Placebo QOW + MTX	14.5	8.1	4.8
Kavanaugh et al.[47] (Abstract)	Combination therapy – open-label extension of ARMADA	250	6 months additional; 12 months total	40mg QOW + MTX	71.2	50.8	26.0
Van de putte et al.[48] (Abstract)	Monotherapy	544	26 weeks	20mg QOW 20mg QW 40mg QOW 40mg QW Placebo	35.8 39.3 46.0 53.4 19.1	18.9 20.5 22.1 35.0 8.2	8.5 9.8 12.4 18.4 1.8
Keystone et al. [49] (Abstract)	Combination therapy	619	52 weeks	20mg QW + MTX 40mg QOW + MTX Placebo + MTX	54.7 58.9 24.0	37.7 41.5 9.5	20.8 23.2 4.5
Furst et al. [50] (Abstract) STAR trial	Combination therapy	636	24 weeks	40mg QOW + DMARDs Placebo + DMARDs	51.9 34.6	28.9 11.3	14.8 3.5
Burmester et al. [52]	Monotherapy	205	12 months additional (24 month completer analysis)	Adalimumab 40mg QW	76	52	24

APPENDIX II. Dear Healthcare Provider Letters (Attached)

Aventis Pharmaceuticals

October 2003

IMPORTANT PRESCRIBING INFORMATION

Dear Healthcare Professional:

Aventis Pharmaceuticals wants to keep you informed of important updates to the safety information for Arava® (leflunomide) tablets. Arava® is indicated in adults for the treatment of active rheumatoid arthritis (RA) to reduce signs and symptoms, inhibit structural damage as evidenced by x-ray erosions and joint space narrowing, and, now, also, to improve physical function, an expanded indication recently approved by the FDA.

In postmarketing experience worldwide, rare, serious, hepatic injury, including cases with fatal outcome, have been reported during treatment with Arava®. Most cases occur within 6 months of therapy and in a setting of multiple risk factors for hepatotoxicity. It should be emphasized that multiple confounding factors were present in most of the cases, such as preexisting hepatic disease, comorbid illness predisposing to hepatic complications, and concomitant potentially hepatotoxic medications.

Rare postmarketing reports of severe infections including sepsis, which may be fatal, have also been received. Most of the reports were confounded by concomitant immunosuppressant therapy and/or comorbid illness, which, in addition to rheumatoid disease, may predispose patients to infection.

As part of postmarketing pharmacovigilance, Aventis Pharmaceuticals has updated the prescribing information and monitoring recommendations to include these rare, serious adverse events.

The **WARNINGS - Hepatotoxicity** section of the prescribing information provides further guidance regarding duration of the initial monthly liver enzyme monitoring, intervals for monitoring in the maintenance of treatment, and dose discontinuation for confirmed ALT elevations more than 3 times the upper limit of normal (ULN). The following revised paragraphs are shown:

> **Hepatotoxicity**
> RARE CASES OF SEVERE LIVER INJURY, INCLUDING CASES WITH FATAL OUTCOME, HAVE BEEN REPORTED DURING TREATMENT WITH LEFLUNOMIDE. MOST CASES OF SEVERE LIVER INJURY OCCUR WITHIN 6 MONTHS OF THERAPY AND IN A SETTING OF MULTIPLE RISK FACTORS FOR HEPATOTOXICITY (liver disease, other hepatotoxins) (see PRECAUTIONS).

Aventis Pharmaceuticals · 300 Somerset Corporate Boulevard · Bridgewater, NJ 08807-2854
Telephone (908) 243-6000 · www.aventis.com

At minimum, ALT (SGPT) must be performed at baseline and monitored initially at monthly intervals during the first 6 months then, if stable, every 6 to 8 weeks thereafter. In addition, if Arava® and methotrexate are given concomitantly, ACR guidelines for monitoring methotrexate liver toxicity must be followed with ALT, AST, and serum albumin testing monthly.

Guidelines for dose adjustment or discontinuation based on the severity and persistence of ALT elevation are recommended as follows: For confirmed ALT elevations between 2- and 3-fold ULN, dose reduction to 10mg/day may allow continued administration of Arava® under close monitoring. If elevations between 2- and 3-fold ULN persist despite dose reduction or if ALT elevations of >3-fold ULN are present, Arava® should be discontinued and cholestyramine or charcoal should be administered (see PRECAUTIONS - General – Need for Drug Elimination) with close monitoring, including retreatment with cholestyramine or charcoal as indicated.

In a 6-month study of 263 patients with persistent active RA despite methotrexate therapy, and with normal LFTs, leflunomide was added to a group of 133 patients starting at 10 mg per day and increased to 20 mg as needed. An increase in ALT greater than or equal to 3 times the ULN was observed in 3.8% of patients compared with 0.8% in 130 patients continued on methotrexate with placebo added.

The **WARNINGS – Immunosuppression Potential/Bone Marrow Suppression** section has additional narrative, as shown below, to emphasize that interruption of therapy with Arava® may be necessary if a serious infection occurs while on Arava®. This follows the previous warning that Arava® is not recommended for patients with severe immunodeficiency, bone marrow dysplasia, or severe, uncontrolled infections.

In the event that a serious infection occurs, it may be necessary to interrupt therapy with Arava® and administer cholestyramine or charcoal (see PRECAUTIONS – General – Need for Drug Elimination). Medications like leflunomide that have immunosuppresion potential may cause patients to be more susceptible to infections, including opportunistic infections. Rarely, severe infections including sepsis, which may be fatal, have been reported in patients receiving Arava®. Most of the reports were confounded by concomitant immunosuppressant therapy and/or comorbid illness, which, in addition to rheumatoid disease, may predispose patients to infection.

There have been rare reports of pancytopenia, agranulocytosis, and thrombocytopenia in patients receiving Arava® alone. These events have been reported most frequently in patients who received concomitant treatment with methotrexate or other immunosuppressive agents, or who had recently discontinued these therapies; in some cases, patients had a prior history of a significant hematologic abnormality.

Patients taking Arava® should have platelet, white blood cell count, and hemoglobin or hematocrit monitored at baseline and monthly for 6 months following initiation of therapy and every 6- to 8 weeks thereafter. If used with concomitant methotrexate and/or other potential immunosuppressive agents, chronic monitoring should be monthly. If evidence of bone marrow suppression occurs in a patient taking Arava®, treatment with Arava® should be stopped, and cholestyramine or charcoal should be used to reduce the plasma concentration of leflunomide active metabolite (see PRECAUTIONS – General – Need for Drug Elimination).

The **PRECAUTIONS - Laboratory Tests** section has been updated with the same monitoring information updated in the **WARNINGS - Hepatotoxicity** section and in the **Immunosuppression Potential/Bone Marrow Suppression** section as discussed above.

The **ADVERSE REACTIONS** section has also been modified to reflect these safety updates.

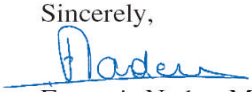
The **CLINICAL STUDIES** section has been updated to include information on physical function and maintenance of effect.

We hope this information will be helpful to you in caring for your patients with RA. From September 1998, when Arava® was approved in the US, through September 2002, approximately 580,000 patients have been treated with Arava® worldwide.[1] The overall safety profile and postmarketing experience with Arava® otherwise remain consistent with the safety and efficacy demonstrated in our extensive clinical-trial program.

Please see the enclosed prescribing information. For more information about the revised prescribing information, please contact Aventis Pharmaceuticals Medical Information Services at (800) 633-1610.

We rely on detailed medical feedback from prescribers to effectively delineate the issues described above and update the general safety profile of our products. You can assist in monitoring the safety of Arava® by reporting all adverse events to the Aventis Pharmaceuticals Medical Information Services at (800) 633-1610; or to the FDA MEDWATCH program: by phone at (800) FDA-1088; by fax at (800) FDA-0178; via the MEDWATCH Web site at www.fda.gov/medwatch; or by mail (using postage-paid form) at: MEDWATCH, HF-2 5600 Fishers Lane, Rockville, MD 20857-9787.

Sincerely,



Francois Nader, MD, MBA
Senior Vice President, Medical Affairs North America
Aventis Pharmaceuticals

1. Data on file. Aventis Pharmaceuticals.

ARA-LT-10773-1

WYETH-AYERST LABORATORIES
P.O. Box 8299
Philadelphia, PA 19101-8299

IMMUNEX®
51 University Street
Seattle, WA 98101-2936

May 11, 1999

Important Drug Warning

Dear Healthcare Professional:

This communication is to inform you of important post-marketing safety information for ENBREL® (etanercept), a new treatment for moderate to severe rheumatoid arthritis. Some of this safety information was already described in the package insert. The new information provides additional data on serious infections reported with the use of ENBREL. Over the five month period following the drug's approval in November 1998, thirty of the estimated 25,000 patients treated with ENBREL are reported to have developed serious infections including several with sepsis. Six of these patients died within two to sixteen weeks after initiation of treatment. In addition to their rheumatoid arthritis, a number of these patients had a history of chronic or recurrent infections, pre-existing infections, diabetes mellitus or other conditions that predisposed them to infections. Infections, including serious infections, are more common in the rheumatoid arthritis population than in the general public.

Based on the current information, we ask you consider the following recommendations regarding the use of ENBREL.

Patients who develop a new infection while undergoing treatment with ENBREL should be monitored closely. Treatment with ENBREL should be discontinued in patients with serious infections, or sepsis.

Treatment with ENBREL should not be initiated in patients with active infections including chronic or localized infections. Physicians should exercise caution when considering the use of ENBREL in patients with a history of recurring infections or with underlying conditions, which may predispose patients to infections such as advanced or poorly controlled diabetes.

The Warnings, Precautions, and Adverse Events sections of the labeling for ENBREL have been revised to incorporate this new information and these revised sections are included in the attached sheet.

A revised package insert is enclosed. Should you have questions regarding the use of ENBREL, please call Wyeth-Ayerst at 1-800-934-5556.

Healthcare professionals should report any serious adverse events possibly associated with the use of ENBREL to Wyeth-Ayerst at 1-800-934-5556. Alternatively, this information may also be reported to FDA's MedWatch reporting system by phone (1-800-FDA-1088), Fax (1-800-FDA-0178), via the MedWatch website at www.fda.gov/medwatch, or by mail (using postage paid form) to MedWatch, HF-2, 5600 Fishers Lane, Rockville, MD 20852-9787. Healthcare professionals and consumers should use the Form 3500 for adverse event/product problem reporting.

Sincerely,

Philip de Vane, M.D.
Vice President, Clinical Affairs
North American Medical Director
Wyeth-Ayerst Laboratories

F. Ann Hayes, M.D.
Senior Vice President
Medical Development
Immunex Corporation

Revised Sections for ENBREL® (etanercept) Package Insert

WARNINGS

IN POST-MARKETING REPORTS, SERIOUS INFECTIONS AND SEPSIS, INCLUDING FATALITIES, HAVE BEEN REPORTED WITH THE USE OF ENBREL. MANY OF THESE SERIOUS EVENTS HAVE OCCURRED IN PATIENTS WITH UNDERLYING DISEASES THAT IN ADDITION TO THEIR RHEUMATOID ARTHRITIS COULD PREDISPOSE THEM TO INFECTIONS. PATIENTS WHO DEVELOP A NEW INFECTION WHILE UNDERGOING TREATMENT WITH ENBREL SHOULD BE MONITORED CLOSELY. ADMINISTRATION OF ENBREL SHOULD BE DISCONTINUED IF A PATIENT DEVELOPS A SERIOUS INFECTION OR SEPSIS. TREATMENT WITH ENBREL SHOULD NOT BE INITIATED IN PATIENTS WITH ACTIVE INFECTIONS INCLUDING CHRONIC OR LOCALIZED INFECTIONS. PHYSICIANS SHOULD EXERCISE CAUTION WHEN CONSIDERING THE USE OF ENBREL IN PATIENTS WITH A HISTORY OF RECURRING INFECTIONS OR WITH UNDERLYING CONDITIONS WHICH MAY PREDISPOSE PATIENTS TO INFECTIONS SUCH AS ADVANCED OR POORLY CONTROLLED DIABETES (SEE PRECAUTIONS, ADVERSE REACTIONS, Infections).

PRECAUTIONS

Immunosuppression

The possibility exists for anti-TNF therapies, including ENBREL, to affect host defenses against infections and malignancies since TNF mediates inflammation and modulates cellular immune responses. In a study of 49 patients with RA treated with ENBREL, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector cell populations. The impact of treatment with ENBREL on the development and course of malignancies, and active and/or chronic infections is not fully understood (see **WARNINGS, ADVERSE REACTIONS, Infections** and **Malignancies**). The safety and efficacy of ENBREL in patients with immunosuppression or chronic infections have not been evaluated.

ADVERSE REACTIONS

Infections

Upper respiratory infections ("colds") and sinusitis were the most frequently reported infections in patients receiving ENBREL or placebo. In placebo-controlled trials, the incidence of upper respiratory tract infections was 16% in the placebo treatment group and 29% in the group treated with ENBREL; and 0.68 events per patient year in the placebo group and 0.82 events per patient year in the group treated with ENBREL when the longer observation of patients on ENBREL was accounted for.

In placebo-controlled trials evaluating ENBREL, no increase in the incidence of serious infections was observed (1.3% placebo, 0.9% ENBREL). In open-label and placebo-controlled trials, 22 serious infections were observed in a total of 745 subjects exposed to ENBREL, including: pyelonephritis, bronchitis, septic arthritis, abdominal abscess, cellulitis, osteomyelitis, wound infection, pneumonia, foot abscess, leg ulcer, diarrhea, sinusitis, and sepsis. Serious infections, including sepsis and death, have also been reported during post-marketing use of ENBREL. Some have occurred within a few weeks after initiating treatment with ENBREL. Many of the patients had underlying conditions (e.g., diabetes, congestive heart failure, history of active or chronic infections) in addition to their rheumatoid arthritis. See **WARNINGS**. Data from a sepsis clinical trial not specifically in patients with RA suggest that ENBREL treatment may increase mortality in patients with established sepsis.[10]

WYETH-AYERST LABORATORIES
P.O. Box 8299
Philadelphia, PA 19101-8299

immunex®
51 University Street
Seattle, WA 98101-2936

October 10, 2000

IMPORTANT DRUG WARNING

Dear Healthcare Professional:

We would like to bring to your attention recent post-marketing reports of adverse events in patients receiving ENBREL® (etanercept). Rare cases of central nervous system disorders, including demyelinating disorders such as multiple sclerosis, myelitis, and optic neuritis, have been reported in patients with rheumatoid arthritis who have received ENBREL therapy. Although the causal relationship to ENBREL therapy remains unclear, other tumor necrosis factor (TNF) antagonists administered to patients with multiple sclerosis have been associated with increases in disease activity[1,2]. Prescribers should exercise caution in considering the use of ENBREL in patients with preexisting or recent-onset central nervous system demyelinating disorders.

In addition, rare cases of pancytopenia, including aplastic anemia, some with a fatal outcome, have been reported in patients with rheumatoid arthritis who have received ENBREL therapy. Although the majority of patients who have developed pancytopenia on ENBREL therapy had recent or concurrent exposure to other anti-rheumatic medications known to be associated with myelosuppression (e.g., methotrexate, leflunomide, azathioprine, and cyclophosphamide), some patients had no recent or concurrent exposure to such therapies. Cases of pancytopenia occurred as early as 2 weeks after initiating ENBREL therapy. The causal relationship to ENBREL therapy remains unclear. Patients should be advised that if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, pallor) while on ENBREL, they should seek immediate medical attention. If significant hematologic abnormalities are identified, consideration should be given to discontinuation of ENBREL therapy.

As a result of these reports, the prescribing information for ENBREL (etanercept) has been revised to include the following new Warning statements.

WARNINGS

Neurologic Events

Rare cases of central nervous system demyelinating disorders have been described in spontaneous adverse event reports (see **ADVERSE REACTIONS**). The causal relationship to ENBREL therapy remains unclear. However, while no clinical trials have been performed evaluating ENBREL therapy in patients with multiple sclerosis, other TNF antagonists administered to patients with multiple sclerosis have been associated with increases in disease activity. Prescribers should exercise caution in considering the use of ENBREL in patients with preexisting or recent-onset central nervous system demyelinating disorders.

Hematologic Events

Rare reports of pancytopenia, including aplastic anemia, some with a fatal outcome, have been reported in patients with rheumatoid arthritis treated with ENBREL (see **ADVERSE REACTIONS**). The causal relationship to ENBREL therapy remains unclear. Although no high risk group has been identified, caution should be exercised in patients being treated with ENBREL who have a previous history of significant hematologic abnormalities. All patients should be advised that if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, pallor) while on ENBREL, they should seek immediate medical attention. If significant hematologic abnormalities are confirmed, consideration should be given to discontinuation of ENBREL therapy.

ENBREL is indicated for reducing signs and symptoms and delaying structural damage in patients with moderately to severely active rheumatoid arthritis. ENBREL is also indicated for reducing signs and symptoms of moderately to severely active polyarticular-course juvenile rheumatoid arthritis in patients who have an inadequate response to one or more DMARDs. ENBREL has been marketed in the U.S.A. since November 1998. Since market introduction, over 80,000 patients have received ENBREL therapy.

A revised package insert is enclosed. Should you have questions regarding the use of ENBREL, please call Immunex at 1 800-466-8639.

Healthcare professionals should report any serious adverse events possibly associated with the use of ENBREL to Immunex at 1 800-466-8639. Alternatively, this information may also be reported to FDA's MedWatch reporting system by phone (1 800-FDA-1088), Fax (1 800-FDA-0178), via the MedWatch website at www.fda.gov/medwatch, or by mail (using postage-paid form) to MedWatch, HF-2, 5600 Fishers Lane, Rockville, MD 20852-9787. Health professionals and consumers should use the Form 3500 for adverse event/product problem reporting.

Sincerely,

Dennis L. Parenti, M.D.
Assistant Vice President
Musculoskeletal, Clinical Affairs
Global Medical Affairs Department
Wyeth-Ayerst Laboratories

George Spencer-Green
Medical Director
Immunex Corporation

References: 1. Van Oosten BW, Barkhof F, Truyen L, et al. Increased MRI activity and immune activation in two multiple sclerosis patients treated with the monoclonal anti-tumor necrosis factor antibody CA2. *Neurology*. 47:1531-4, 1996. 2. Arnason BGW, et al. (Lenercept Multiple Sclerosis Study Group). TNF neutralization in MS: Results of a randomized, placebo-controlled multicenter study. *Neurology*. 53:457-65, 1999.

Enbrel is manufactured by Immunex Corporation, Seattle, WA 98101 and is marketed by Immunex Corporation and Wyeth-Ayerst Pharmaceuticals.

Centocor

October 5, 2001

IMPORTANT DRUG WARNING

Dear Healthcare Professional:

Centocor would like to inform you of important safety information for REMICADE® (infliximab), a biological therapeutic product indicated for the treatment of rheumatoid arthritis and Crohn's disease. Tuberculosis, and other serious opportunistic infections including histoplasmosis, listeriosis, and pneumocystosis, have been reported in both the clinical research and post-marking surveillance settings. Some of these infections have been fatal. Accordingly, Centocor has added a Boxed Warning to the labeling for the product and the Warnings and Adverse Reactions sections of the product labeling were revised on August 8, 2001.

The Boxed Warning was added as a result of the occurrence of 84 cases of tuberculosis worldwide, during the period from August 24th, 1998, through June 30th, 2001. Many of the cases reported were disseminated or extrapulmonary at the time of clinical presentation. Of the 84 cases, fourteen were reported to have died, although the primary cause of death was not always reported as TB. Most cases of TB were diagnosed within seven months of the initiation of REMICADE therapy and most reported the use of concomitant immunosuppressive medications. An increased risk of infections associated with tumor necrosis factor (TNF) blockade, is consistent with the known effects of TNF on macrophage activation and granuloma formation. Thus far, approximately 170,000 patients have been treated worldwide with REMICADE.

Clinicians are advised to carefully review the revisions to the labeling (see *BOXED WARNING*, *WARNINGS, PRECAUTIONS,* and *ADVERSE REACTIONS* sections of the labeling), which are summarized below. A copy of the full prescribing information is also enclosed.

The Boxed *WARNING* now contains the following information:

Tuberculosis (frequently disseminated or extrapulmonary at clinical presentation), invasive fungal infections, and other opportunistic infections, have been observed in patients receiving REMICADE. Some of these infections have been fatal (see *WARNINGS*).

Patients should be evaluated for latent tuberculosis infection with a tuberculin skin test.[1] Treatment of latent tuberculosis infection should be initiated prior to therapy with REMICADE.

Centocor, Inc. •200 Great Valley Parkway•Malvern, Pennsylvania 19355-1307 •Telephone (610) 651-6000•Facsimile (610) 651-6100

Additionally, the following new warning has been added to the package insert:

CASES OF HISTOPLASMOSIS, LISTERIOSIS, PNEUMOCYSTOSIS AND TUBERCULOSIS, HAVE BEEN OBSERVED IN PATIENTS RECEIVING REMICADE. FOR PATIENTS WHO HAVE RESIDED IN REGIONS WHERE HISTOPLASMOSIS IS ENDEMIC, THE BENEFITS AND RISKS OF REMICADE TREATMENT SHOULD BE CAREFULLY CONSIDERED BEFORE INITIATION OF REMICADE THERAPY.

Centocor will make available patient information that informs patients of the potential safety risks possibly associated with REMICADE® (infliximab).

Centocor is committed to ensuring that REMICADE is used safely and effectively and is working closely with healthcare professionals to communicate the most recent labeling change. Centocor is also working to educate all healthcare professionals on minimizing the risk of active tuberculosis infection by taking appropriate measures to screen and treat for latent TB infection.

Centocor is committed to providing you with the most current product information for REMICADE. You can assist us with monitoring the safety of REMICADE by reporting adverse events to Centocor at 1-800-457-6399. Alternatively, this information may be reported to FDA's MedWatch reporting system by phone (1-800-FDA-1088), facsimile (1-800-FDA-0178), the MedWatch website at www.fda.gov/medwatch, or mailed to MedWatch, HF-2, 5600 Fishers Lane, Rockville, MD 20852-9787. Both healthcare professionals and consumers should use Form 3500 for reporting adverse events.

Should you have any questions or require further information regarding the use of REMICADE, please contact Centocor's Medical Affairs Department at 1-800-457-6399.

Sincerely,

Thomas F. Schaible, PhD
Executive Director, Medical Affairs

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[1] American Thoracic Society, Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. *Am J Respir Crit Care Med* 2000;161:S221-S247

Centocor, Inc. •200 Great Valley Parkway•Malvern, Pennsylvania 19355-1307•Telephone (610) 651-6000•Facsimile (610) 651-6100

October 18, 2001

IMPORTANT DRUG WARNING

Dear Healthcare Professional:

Centocor, Inc. would like to inform you of important new safety information for REMICADE® (infliximab). Upon review of preliminary results of its ongoing phase 2 trial in 150 patients with moderate to severe (NYHA class III-IV) congestive heart failure (CHF), higher incidences of mortality and hospitalization for worsening heart failure were seen in patients treated with REMICADE, especially those treated with the higher dose of 10 mg/kg. Seven of 101 patients treated with REMICADE died compared to no deaths among the 49 patients on placebo.

In this trial, stable but symptomatic patients with NYHA Class III-IV CHF were treated with 3 infusions of REMICADE 5 mg/kg, REMICADE 10 mg/kg, or placebo over 6 weeks. REMICADE is a biological therapeutic product indicated for the treatment of rheumatoid arthritis and Crohn's disease.

Centocor, in consultation with FDA, is alerting physicians to these potential adverse effects of REMICADE in patients with CHF. At present, there are insufficient data to determine optimal patient management. However, based on these preliminary findings, and pending additional data, physicians should consider the following precautionary measures.

For patients with rheumatoid arthritis or Crohn's disease being considered for therapy with REMICADE:

- Do not initiate therapy in patients with congestive heart failure.

Patients with CHF currently receiving chronic REMICADE treatment for rheumatoid arthritis or Crohn's disease should be reevaluated.

- Treatment should be discontinued in patients whose CHF is worsening.

- Treatment discontinuation should be considered in patients with stable concomitant CHF, especially in those who have not had a significant clinical response to REMICADE therapy. If a decision is made to continue treatment, cardiac status should be closely monitored.

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Although experimental pre-clinical studies and prior small clinical trials had suggested that therapy targeted at TNF might be of benefit in patients with CHF, this and other recent trials have failed to demonstrate that agents that bind TNF can improve the clinical course in these patients.

Centocor will continue to acquire follow up data on patients in the phase 2 trial in order to better characterize the risk posed by REMICADE® (infliximab) to patients with CHF and to provide more definitive conclusions and recommendations to healthcare professionals, in the form of a future update to the prescribing information.

Centocor is committed to ensuring that REMICADE is used safely and effectively and will continue to work closely with the FDA and healthcare professionals to communicate new information and updates to the prescribing information concerning the potential for risk associated with the use of REMICADE in patients with concomitant CHF.

Centocor can assure you that it will provide you with the most current product information for REMICADE. You can assist us with monitoring the safety of REMICADE by reporting adverse events to Centocor at 1-800-457-6399. Alternatively, this information may be reported to FDA's MedWatch reporting system by phone (1-800-FDA-1088), facsimile (1-800-FDA-0178), the MedWatch website at www.fda.gov/medwatch, or mailed to MedWatch, HF-2, 5600 Fishers Lane, Rockville, MD 20852-9787. Both healthcare professionals and consumers should use Form 3500 for reporting adverse events.

Should you have any questions or require further information regarding the use of REMICADE, please contact Centocor's Medical Affairs Department at 1-800-457-6399.

Sincerely,

Lawrence I. Deckelbaum, MD
Executive Director
Cardiac, Vascular and Pulmonary
Clinical Research and Development

Centocor

11 August 2004

IMPORTANT DRUG WARNING

Dear Healthcare Professional:

Centocor would like to inform you of important safety information concerning hematologic and neurologic events for REMICADE® (infliximab), a biological therapeutic product indicated for the treatment of rheumatoid arthritis and Crohn's disease.

In postmarketing experience worldwide, hematologic events including leukopenia, neutropenia, thrombocytopenia and pancytopenia, some with a fatal outcome, have been reported in patients receiving REMICADE. Accordingly, Centocor has added a Warning on Hematologic Events to the labeling for the product as follows:

> **Hematologic Events**
>
> Cases of leukopenia, neutropenia, thrombocytopenia, and pancytopenia, some with a fatal outcome, have been reported in patients receiving REMICADE. The causal relationship to REMICADE therapy remains unclear. Although no high-risk group(s) has been identified, caution should be exercised in patients being treated with REMICADE who have ongoing or a history of significant hematologic abnormalities. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever) while on REMICADE. Discontinuation of REMICADE therapy should be considered in patients who develop significant hematologic abnormalities.

In addition, the Warning on Neurologic Events has been updated (see Warnings in the enclosed prescribing information) to:

- describe rare cases of CNS manifestation of systemic vasculitis; and
- warn that discontinuation of REMICADE should be considered in patients who develop significant central nervous system adverse reactions.

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Finally, the Adverse Reaction sections of the REMICADE prescribing information has been updated to add the following adverse events that have been reported during post-approval use of REMICADE: neutropenia, pericardial effusion and systemic and cutaneous vasculitis.

Since August 24, 1998, when REMICADE was approved in the US, approximately 509,000 patients have been treated with REMICADE worldwide.

Enclosed please find the updated prescribing information as well as the patient information sheet.

Centocor is committed to ensuring that REMICADE is used safely and effectively and is committed to providing you with the most current product information for REMICADE. You can assist us with monitoring the safety of REMICADE by reporting adverse events to Centocor at 1-800-457-6399. Alternatively, this information may be reported to FDA's MedWatch reporting system by phone (1-800-FDA-1088), facsimile (1-800-FDA-0178), the MedWatch website at www.fda.gov/medwatch, or mailed to MedWatch, HF-2, 5600 Fishers Lane, Rockville, MD 20852-9787. Both healthcare professionals and consumers should use Form 3500 for reporting adverse events.

Should you have any questions or require further information regarding the use of REMICADE, please contact Centocor's Medical Affairs Department at 1-800-457-6399.

Sincerely,

Daniel Everitt, MD
Vice President,
Clinical Pharmacology and Global Pharmacovigilance
Centocor, Inc.

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October 2004

IMPORTANT DRUG WARNING

Dear Healthcare Professional:

Centocor, Inc., would like to inform you of important safety information concerning malignancies for REMICADE® (infliximab), a biological therapeutic product indicated for the treatment of rheumatoid arthritis and Crohn's disease.

The Food and Drug Administration (FDA) convened its Arthritis Advisory Committee in March 2003 to review and advise on safety data for marketed tumor necrosis factor (TNF) blockers, including REMICADE. A particular focus was placed on the incidence of neoplasia and lymphoma in patients receiving these agents. Safety data from controlled clinical trials and post-marketing experience were examined. As a result of this evaluation, a warning concerning malignancy has been added to the labeling for all therapeutic agents that block TNF.

Centocor, in consultation with the FDA, has added a Warning to the labeling for REMICADE as follows:

WARNINGS - Malignancies

In the controlled portions of clinical trials of all the TNFα-blocking agents, more cases of lymphoma have been observed among patients receiving a TNF blocker compared with control patients. During the controlled portions of REMICADE trials in patients with moderately to severely active rheumatoid arthritis and Crohn's disease, 1 patient developed lymphoma among 1389 REMICADE-treated patients versus 0 among 483 control patients (median duration of follow-up 1.1 years). In the controlled and open-label portions of these clinical trials of REMICADE, 3 patients developed lymphomas (1 patient with rheumatoid arthritis and 2 patients with Crohn's disease) among 2410 patients (median duration of follow-up 1.1 years). In rheumatoid arthritis patients, this is approximately 3-fold higher than expected in the general population. In the combined clinical trial population for rheumatoid arthritis and Crohn's disease, this is approximately 6-fold higher than expected in the general population. Rates in clinical trials for REMICADE cannot be compared to rates of clinical trials of other TNF blockers and may not predict rates observed in a broader patient population. Patients with Crohn's disease or rheumatoid arthritis, particularly patients with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for the development of lymphoma. The potential role of TNFα-blocking therapy in the development of malignancies is not known (see ADVERSE REACTIONS, Malignancies). No studies have been conducted that include patients with a history of malignancy or that continue treatment in patients who develop malignancy while receiving REMICADE; thus additional caution should be exercised in considering REMICADE treatment of these patients.

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Also, the Adverse Reaction section of the REMICADE® (infliximab) prescribing information has been updated to add the following section on malignancies.

ADVERSE REACTIONS – Malignancies

Among 2410 patients with moderately to severely active rheumatoid arthritis and Crohn's disease treated with REMICADE in clinical trials with a median of 1.1 years of follow-up, 3 patients developed lymphomas, for a rate of 0.07 cases per 100 patient-years of follow-up in patients with rheumatoid arthritis and 0.12 cases per 100 patient-years of follow up in the combined clinical trial data for rheumatoid arthritis and Crohn's disease patients. This is approximately 3-fold higher in the RA clinical trial population and 6-fold higher in the overall clinical trial population than expected in an age-, gender-, and race-matched general population based on the Surveillance, Epidemiology and End Results Database. Rates in clinical trials for REMICADE cannot be compared to rates of clinical trials of other TNF blockers and may not predict rates observed in a broader patient population. An increased rate of lymphoma up to several fold has been reported in the Crohn's disease and rheumatoid arthritis patient populations, and may be further increased in patients with more severe disease activity. Other than lymphoma, 13 patients developed malignancies, which was similar in number to what would be expected in the general population. Of these, the most common malignancies were breast, colorectal, and melanoma. (See WARNINGS, Malignancies.)

Malignancies, including non-Hodgkin's lymphoma and Hodgkin's disease, have also been reported in patients receiving REMICADE during post-approval use.

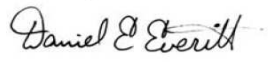
Since August 24, 1998, when REMICADE was approved in the United States, approximately 576,000 patients have been treated with REMICADE worldwide.

Enclosed please find the updated prescribing information as well as the patient information sheet.

Centocor is committed to ensuring that REMICADE is used safely and effectively and is committed to providing you with the most current product information for REMICADE. You can assist us with monitoring the safety of REMICADE by reporting adverse events to Centocor at 1-800-457-6399. Alternatively, this information may be reported to FDA's MedWatch reporting system by phone (1-800-FDA-1088), facsimile (1-800-FDA-0178), the MedWatch website at www.fda.gov/medwatch, or mailed to MedWatch, HF-2, 5600 Fishers Lane, Rockville, MD 20852-9787. Both healthcare professionals and consumers should use Form 3500 for reporting adverse events.

Should you have any questions or require further information regarding the use of REMICADE, please contact Centocor's Medical Affairs Department at 1-800-457-6399.

Sincerely,



Daniel E. Everitt, M.D.
Vice President,
Clinical Pharmacology and Global Pharmacovigilance
Centocor, Inc.
enclosure

 10/04 IN04569

December 2004

IMPORTANT DRUG WARNING

Dear Healthcare Professional:

Centocor would like to inform you of important updates to the prescribing information for REMICADE® (infliximab), including the addition of a Warning on hepatotoxicity and an update to the existing Warning on Risk of Infections. REMICADE is a biological therapeutic product indicated for the treatment of rheumatoid arthritis, Crohn's disease and, most recently, ankylosing spondylitis.

In postmarketing experience worldwide, severe hepatic reactions including acute liver failure, jaundice/cholestasis, and hepatitis, including autoimmune hepatitis, have been rarely reported in patients receiving REMICADE. Since August 24, 1998, when REMICADE was approved in the US, approximately 576,000 patients have been treated with REMICADE worldwide. Approximately 3 patients in controlled clinical trials and 35 patients in the voluntary postmarketing reported events are considered to be severe hepatic reactions. A causal relationship between REMICADE and these events has not been established.

Centocor has added a Warning on Hepatotoxicity to the labeling for the product as follows:

WARNINGS: Hepatotoxicity

> Severe hepatic reactions, including acute liver failure, jaundice, hepatitis and cholestasis, have been reported rarely in postmarketing data in patients receiving REMICADE. Autoimmune hepatitis has been diagnosed in some of these cases. Severe hepatic reactions occurred between two weeks to more than a year after initiation of REMICADE; elevations in hepatic aminotransferase levels were not noted prior to discovery of the liver injury in many of these cases. Some of these cases were fatal or necessitated liver transplantation. Patients with symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If jaundice and/or marked liver enzyme elevations (e.g., ≥5 times the upper limit of normal) develops, REMICADE should be discontinued, and a thorough investigation of the abnormality should be undertaken. As with other immunosuppressive drugs, use of REMICADE has been associated with reactivation of hepatitis B in patients who are chronic carriers of this virus (i.e.,

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surface antigen positive). Chronic carriers of hepatitis B should be appropriately evaluated and monitored prior to the initiation of and during treatment with REMICADE. In clinical trials, mild or moderate elevations of ALT and AST have been observed in patients receiving REMICADE without progression to severe hepatic injury (see ADVERSE REACTIONS, Hepatotoxicity).

The Adverse Reactions section and Patient Information Sheet were also updated to include important information regarding hepatotoxicity (see enclosed prescribing information).

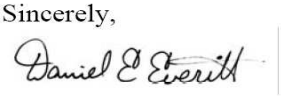
In addition, Centocor has added pneumonia to the existing Warnings on Risk of Infections based on clinical trial data in RA patients described in the Adverse Reactions section of the labeling.

Enclosed please find the updated prescribing information as well as the patient information sheet.

Centocor is committed to ensuring that REMICADE is used safely and effectively and is committed to providing you with the most current product information for REMICADE. You can assist us with monitoring the safety of REMICADE by reporting adverse events to Centocor at 1-800-457-6399. Alternatively, this information may be reported to FDA's MedWatch reporting system by phone (1-800-FDA-1088), facsimile (1-800-FDA-0178), the MedWatch website at www.fda.gov/medwatch, or mailed to MedWatch, HF-2, 5600 Fishers Lane, Rockville, MD 20852-9787. Both healthcare professionals and consumers should use Form 3500 for reporting adverse events.

Should you have any questions or require further information regarding the use of REMICADE, please contact Centocor's Medical Affairs Department at 1-800-457-6399.

Sincerely,



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APPENDIX III. Pharmacoeconomic Findings

Reference	Treatments Compared	Effectiveness Data Source	Health State Valuations	Perspective	Costs	Time Horizon	Rate of Discount	Economic Model
Maetzel et al. [75]	DMARD treatment sequence (MTX; MTX, SSZ; MTX, SSZ, HCQ; Gold; Cyclosporine); DMARD treatment sequence with leflunomide (MTX; MTX, SSZ; MTX, SSZ, HCQ; Leflunomide; Gold; Cyclosporine)	RCT [2]; Observational Studies	Standard gamble and rating scale utilities; ACR20	Public payer	Direct	5 years	3% (costs and QALYs)	Decision Analysis
Maetzel et al. [76]	Leflunomide (20mg/day); placebo; MTX (15mg/week)	RCT [2]	Standard gamble and rating scale utilities	Societal	Direct and Indirect	1 year	Not reported	Economic data collected concurrently with RCT
Welsing et al. [77]	1) Usual treatment; 2) Treatment with leflunomide; if no response after 3 months, switch to usual treatment; 3) Treatment with TNF inhibitor; if no response after 3 months, switch to usual treatment; 4) Treatment with leflunomide; if no response after 3 months, switch to TNF inhibitors; if no response after 3 months, switch to usual treatment; 5) Treatment with TNF inhibitors; if no response after 3 months, switch to leflunomide; if no response after 3 months, switch to usual treatment	Follow-up data from open study; dataset from Wyeth Pharmaceuticals; RCT [3]	EuroQoL Questionnaire	Societal and third party payer	Direct and Indirect	5 years	4% (costs and effects)	Markov Model
Choi et al. [78]	Etanercept + MTX; Etanercept monotherapy; Cyclosporine monotherapy; HCQ, SSZ, MTX; MTX monotherapy; no second-line agent	RCT [13, 14, 79, 80]	ACR20; ACR70WR	Societal	Direct and Indirect	6 months	None	Decision tree
Choi et al. [81]	Etanercept; Leflunomide; MTX; SSZ; no second-line agent	RCT [2, 5, 6, 16]	ACR20; ACR70WR	Societal	Direct and Indirect	6 months	None	Decision tree
Brennan et al. [82]	Etanercept as 3rd-line therapy; sequence of 3 traditional nonbiologic DMARDs (IM Gold, leflunomide, or cyclosporine +MTX as 3rd, 4th, and 5th-line agents	RCT [13]	HAQ scores converted to QALYs using published regression of HAQ vs. EuroQol (EQ-5D)-derived utility	Healthcare payer in the UK	Direct	Lifetime	6% (costs); 1.5% (effects)	Individual patient simulation model; Monte Carlo simulation samples whether the patient survives the 6-month period
Kobelt et al. [83]	Etanercept; Infliximab	Observational follow-up registry in	EQ-5D	Societal	Direct and Indirect	1 year	None	Changes in outcomes and cost compared to

		southern Sweden; RCT [84]						year before treatment
Kobelt et al. [85]	Etanercept 25mg subcutaneously twice weekly x 2 years; MTX 20mg every week x 2 years; Etanercept +MTX x 2 years	RCT [86]	EQ-5D; regression HAQ	Societal	Direct and Indirect	10 years	3% (costs and effects)	Markov model
Wong et al. [87]	MTX+Infliximab; MTX monotherapy; DMARD monotherapy; MTX + DMARD; steroid + NSAID	RCT [25, 27] ARAMIS database [88]	VAS	Societal	Direct and Indirect	Lifetime	3% (costs)	Markov Model
Kobelt et al. [89]	Infliximab +MTX; MTX alone	RCT [25] Cohort studies [90-95]	EQ-5D	Societal	Direct and Indirect	10 years	3%, 6% (costs); 3%, 1.5% (QALY)	Markov Model
Bansback et al. [96]	Adalimumab; traditional DMARDs	RCT [13, 14, 25, 46, 48] Observational studies [84, 97]	HUI-III; ACR20/moderate DAS28 response; ACR50/good DAS28 response	Policy maker	Direct	Lifetime	3% (costs and benefits)	Mathematic probabilistic model implementing a patient-based transition state model that allows feedback loops between key variables after response and withdrawal of treatment
Guh et al. [98]	Low dose (1mg/kg) anakinra+MTX; high dose (2mg/kg) anakinra+MTX; MTX alone	RCT	HUI-III, ACR20	Societal	Direct and Indirect	1 year	Not reported	Decision analytic model

DMARD = Disease Modifying Antirheumatic Drug; MTX = Methotrexate; SSZ = Sulfasalazine; HCQ = Hydroxychloroquine; IM = Intramuscular; RCT = Randomized Controlled Trial; ACR = American College of Rheumatology; DAS = Disease Activity Score; HAQ = Health Assessment Questionnaire; EQ-5D = EuroQol questionnaire; VAS = Visual Analogue Scale; HUI = Health Utilities Index; QALY = Quality Adjusted Life Year

Summary of Pharmacoeconomic Findings

There are few published cost effectiveness analyses of leflunomide and the biologic DMARDs. Included in the table above are published analyses where cost effectiveness was measured via modeling of direct and/or indirect costs with efficacy, quality of life, or functional status of RA patients. Eleven publications examining the costs and benefits of leflunomide, etanercept, infliximab, and/or adalimumab were identified. One abstract for anakinra was included as no fully published economic evaluations were available.

Superficially, the analyses demonstrate potential cost effectiveness. Studies investigating the cost effectiveness of leflunomide suggest that leflunomide may extend the time that patients may benefit from DMARD therapy and that patients receiving leflunomide have a more positive perception of their health; but leflunomide becomes more expensive when monitoring and drug acquisition costs are included.[75-77] Fully published pharmacoeconomic studies in the US show etanercept to have a place in the management of DMARD-naïve and DMARD-resistant patients with RA at a higher incremental cost per ACR20 or ACR70WR than other options analyzed, but the cost effectiveness depends on whether the cost utility and cost effective ratios are acceptable in specific settings. [78, 81] Studies of adults in the UK and Sweden propose that etanercept and etanercept+MTX, respectively, are associated with acceptable cost utility ratios versus comparators. [82, 85] In patients with RA who have not responded to previous MTX or other DMARD therapy, infliximab has resulted in acceptable cost-utility ratios. [87, 89] A cost effectiveness analysis involving adalimumab conveys that adalimumab is at least as cost effective as other TNF antagonists in patients with moderate to severe RA in Sweden. [96] Data from an abstract indicates high incremental cost effectiveness ratios for anakinra compared with methotrexate and attribute this to the acquisition costs of anakinra. [98]

A closer look at the pharmacoeconomic studies and their methodologies reveal limitations regarding:

1) Appropriate time horizon.

RA is a chronic disease. As such, duration of disease should be modeled over a clinically relevant period, with at least a 1 year time horizon for continuous RA therapy. These cost effective analyses have studied time horizons ranging from 6 months to lifetime. Modeling duration of disease beyond 1 year is attractive for policy making decision purposes, but may increase uncertainty as parameters associated with those time horizons must then rely on assumptions since long-term effectiveness data from randomized, controlled, clinical trials is limited.

2) Extrapolating randomized controlled trial results beyond 1 year.

   As insufficient data is available from long term randomized controlled studies, short term randomized controlled trial data is combined with long term observational cohort data in order to model cost effectiveness over an appropriate time horizon. In doing this, investigators must make assumptions concerning the continuation/withdrawal of therapy, path of disease after discontinuation, and outcomes/quality of life ensuing after drug treatment. These assumptions increase uncertainty in modeling estimates.

3) Combining short-term randomized controlled trial with long term observational cohort data to model cost effectiveness over a more extended time horizon.

   When merging data from different sources, it is important that the patient groups are of similar type and have similar disease characteristics to ensure homogeneity of the study population.

4) Validity of the health outcome measure.

   There is no consensus measure of response, and improvement is reported using various methods. ACR is an appropriate marker for improvement in randomized controlled trials, but does not necessarily represent effectiveness in real clinical practice. The DAS is a validated composite score that integrates several components of inflammation and is used in much of Europe. On the other hand, the HAQ is a common global heath outcome measure and preference-based measures can be derived from manipulating HAQ scores via linear regression.

5) Population stratification.

   Economic models should consider patients' baseline characteristics since these risk factors will define their treatment or sequence of treatments as standard of care is unlikely to be a single treatment, or the same for each patient. Subgroup analyses could have been explored to examine how covariates (such as duration of disease and therapeutic treatment) can impact the cost effectiveness.

6) Inclusion of negative outcomes.

   Some analyses did not clearly state negative outcomes. Adverse events directly related to a given treatment will influence quality of life and costs (direct and indirect) of the treatment.

In conclusion, diversity in time horizons, comparators, quantities of drugs, discount rates, treatment sequences, and outcome measures make it difficult to compare cost-effectiveness ratios between the individual analyses. In addition, these cost effective analyses are only pertinent for patient groups similar to the trials in which the agents were studied and are country specific due to differences in health care systems, medical practice, unit costs, and discount rates. The pharmacoeconomic position of one agent over another would be clarified by cost utility and cost effectiveness analyses incorporating data from direct comparative trials or from trials in patients with RA of similar duration and severity. Further cost effectiveness analyses are needed to answer superiority of one treatment over another, sequential use of different TNF inhibitors, and use of treatments earlier in the disease course.

The following recommendations are based on current medical evidence and expert opinion from clinicians. The content of the document is dynamic and will be revised as new clinical data becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient.

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